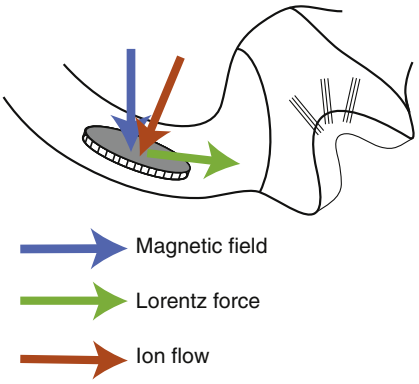

Figure 2. The Lorentz force created in the horizontal semicircular canal arises largely from ionic current flow that is perpendicular to the utricle, and the magnetic field vector. The Lorentz force is given by the cross product of these two vectors and is therefore perpendicular to the plane spanned by the vectors. Depending upon the orientation of the utricle, that is, the position of the head in the scanner, the magnitude of the Lorentz force changes. The Lorentz force deflects the cupular membrane and hair cells of the horizontal canal, producing a vestibular signal of horizontal head rotation.

Roberts *et al.* [5] went one step further to uncover the exact mechanism of MRI-induced eye movements and vertigo in MRI scanners. They tested different hypotheses based on the induced eye drift in different conditions. Dynamic bio-magnetic mechanisms could be discarded, because the ocular drift was permanent as long as the subjects were in the scanner. The only possible static bio-magnetic mechanism that could explain the dependence of the constant vestibulo-ocular response on the polarity and strength of the magnet is a Lorentz force, a force produced by the interaction of an electric current flow and a magnetic field. The endolymph in the vestibular labyrinth has a high concentration of potassium ions, and so carries an ionic current.

From geometric considerations and estimations of force magnitude, Roberts *et al.* [5] localized the MRI-induced Lorentz force mainly at the utricule, a structure that normally detects linear acceleration including gravity (Figure 2). Ions are exchanged between the potassium-rich endolymph and the hair cells [6]; the average net ionic flow at rest enters each utricle perpendicular to its surface, which is pitched upward by about 30 degrees backward with the head in supine position. The interaction between the ionic flow and the magnetic field produces the Lorentz force, which is given by the cross-product between flow and field, and is therefore perpendicular to the plane spanned by the flow and the field. With the head pitched slightly forward from supine, the Lorentz force becomes minimal. The Lorentz force is directed along the horizontal semicircular canal at the level of the cupula. This physiologic pressure sensor is therefore stimulated by the Lorentz force as if the head was rotated with a constant acceleration in the plane of the canal to the left or right [7], depending on the pitch angle and the polarity of the magnet.

The most important ramification of the findings by Roberts *et al.* [5] is that a pure functional MRI resting state usually does not exist, as the magnetic field produces constant vestibular stimulation with ongoing nystagmus and vertigo. As researchers increase the strength of the magnets, this problem becomes more serious. A consequence is that nearly every functional MRI study is contaminated with neural activity related to perception (vertigo) and eye movements (nystagmus) caused by vestibular stimulation. If experiments are performed in the light and subjects have their eyes open, the ocular drift activates the visual system and eye movement areas that suppress the drift. Comparisons of fMRI studies among different laboratories must therefore take into account the strength and polarity of the magnetic field, the position of the head relative to the magnetic field and whether experiments were performed in darkness with ongoing vestibular nystagmus or in the light with visual suppression of nystagmus. Future MRI studies should probably aim to position subject's heads slightly pitched forward, where Roberts *et al.* [5] found the minimal Lorentz force, perhaps even by finding the optimal position for each subject by monitoring nystagmus. This would aid the interpretation of functional MRI studies, as well as increase subject and patient comfort within the scanner.

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Nuclear Architecture: The Cell Biology of a Laminopathy

Lamin mutations cause muscular dystrophies, but the mechanism is unclear. A new study shows that lamin mutant worms display muscle-specific defects linked to altered subnuclear localization of heterochromatin, leading to altered gene expression.

Jason H. Brickner

The nuclear lamina is a fibrous network of proteins associated with the inner nuclear envelope. The primary structural components of this network are the nuclear lamins, intermediate filament proteins that form a very stable

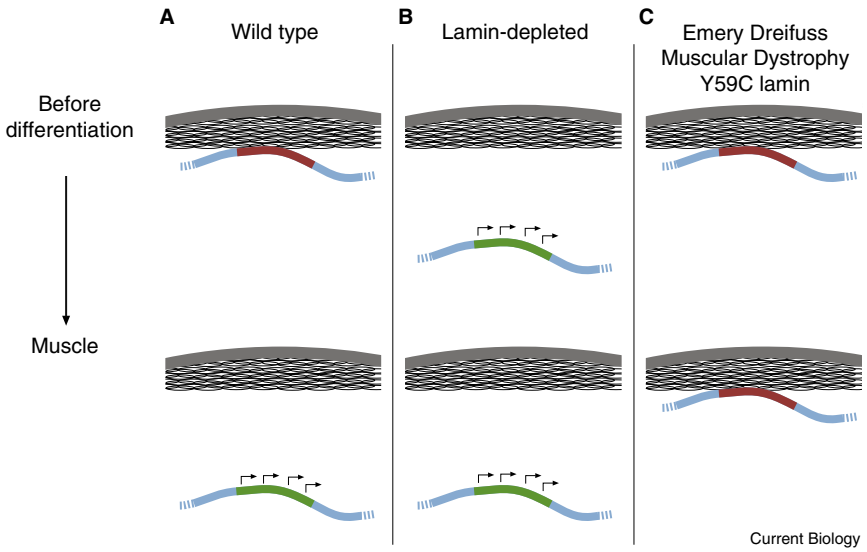

Figure 1. Lamin mutations have different effects on chromatin localization and gene expression in worms.

Schematic representation of integrated plasmid arrays interacting with the nuclear lamina at the nuclear periphery. The lamina is a fibrous mesh under the nuclear envelope. Integrated arrays of plasmids in *C. elegans* localize at the nuclear periphery in wild-type embryos (A), when they are not expressed (red array). After differentiation, a plasmid array having a muscle-specific promoter localizes to the nucleoplasm, where it is expressed (green array). In contrast, in embryos depleted of lamin (B), the plasmid arrays localize in the nucleoplasm and are frequently expressed, inappropriately. In worms expressing Y59C lamin (C), the arrays remain localized at the nuclear periphery after differentiation and are poorly expressed.

filamentous meshwork [1]. The lamina both protects the nucleus from physical stresses and plays a crucial role in the spatial organization of chromatin.

Most heterochromatin is localized at the nuclear periphery and large portions of the genome in worms, flies and mammals contact the nuclear lamina. Such Lamin-Associated Domains (LADs) are gene-poor, poorly expressed and enriched for heterochromatic chromatin modifications [2]. As genes are induced during differentiation, they dissociate from the lamina and move from the nuclear periphery to a more internal location [3,4]. Therefore, the interaction of chromatin with the nuclear lamina has been suggested to promote silencing and heterochromatin formation. Consistent with this idea, the transcription of many genes is repressed by artificially tethering to the lamina [5,6].

Mutations in lamins and lamin-associated proteins lead to many human diseases known collectively as 'laminopathies' [7,8]. These include several muscular dystrophies and myopathies. For example, Emery Dreifuss Muscular Dystophy (EDMD) is caused by mutations in both lamin A/C and a lamin-binding protein and primarily affects skeletal and cardiac muscle. Two models have been proposed to explain the specific degeneration of muscle tissues in these diseases. One model suggests that muscle tissues are subject to extreme mechanical stresses, making them very sensitive to lamin dysfunction. The death of these cells would therefore be a result of DNA damage due to mechanical abuse. An alternative model proposes that muscle defects are due to defective nuclear organization of chromatin, leading to altered gene expression. Whereas the first model provides an explanation for the tissue-specificity, the second does not.

A new paper from the labs of Susan Gasser and Yosef Gruenbaum [9] published in this issue of *Current Biology* provides important new insight into the molecular basis of EDMD. The authors have developed the roundworm *Caenorhabditis elegans* as a model for the disease. Worms possess only a single lamin gene (in which mutants exist), are readily transformed and are famously amenable to RNAi knockdown. The authors sought to explore how either loss of lamin function or a dominant EDMD mutant allele of lamin (equivalent to a Y45C substitution in the human Lamin A/C gene; Y59C in worms) affected the localization and expression of genes embedded in heterochromatin. To address these questions, they utilized a system that the Gasser lab has developed to localize arrays of integrated plasmids in living animals [10]. Plasmids integrate into the worm genome in arrays of hundreds of copies. The plasmids used in this study express the GFP–lac repressor and possess a lac repressor binding site, allowing localization. They also possess an RFP reporter driven from different tissue-specific promoters. The localization of these arrays reflects both their size and the activity of the promoters [10]. Large arrays localize at the nuclear periphery in tissues in which they are not expressed but localize to a more internal site in tissues in which they are expressed (Figure 1). Using this powerful tool, the authors asked how altering the lamina affects the localization and expression of these plasmids.

If laminopathies like EDMD were caused by loss of lamin function through either depletion or dominant negative effects, loss of lamin and expression of the Y59C lamin should have similar phenotypes. However, a null mutant in worm lamin and expression of the EDMD mutant form of lamin had opposite effects [9]. Whereas lamin depletion led to loss of peripheral localization and over-expression of the reporter gene, expression of Y59C lamin caused inappropriate retention of the plasmid array at the nuclear periphery and poor expression of the muscle reporter (Figure 1). These effects were muscle-specific; in the muscle cells of the animals expressing Y59C lamin, a reporter plasmid array having a muscle-specific promoter was retained at the nuclear periphery and its expression was reduced. However, in gut cells, a reporter plasmid array bearing a gut-specific promoter moved from the nuclear periphery to the nuclear interior normally. This suggests that Y59C is a gain-of-function mutation that blocks relocalization of facultative heterochromatin in a tissue-specific fashion.

In addition to the effects on the localization and expression of transgenic arrays of plasmids, expression of the EDMD form of lamin led to defects in muscle function and morphology. Expression of Y59C

significantly reduced the frequency of the back and forth movement of the animals' heads during swimming. This effect was abrogated when the animals were treated with RNAi against the Y59C lamin, indicating that it was a product of the dominant mutant. Furthermore, the Y59C-expressing animals exhibited disorganized actin fibers and sarcomeres in muscle cells. Thus, expression of Y59C lamin affects both nuclear organization of chromatin and muscle cell function, suggesting that the worm system may be a good model for the human pathology.

What is the connection between defective movement of heterochromatin from the nuclear periphery to the nucleoplasm and the muscle-specific defects? The authors note that many genes that are important for muscle biogenesis are located near the ends of chromosomes, within LADs [11], and that several of these genes are poorly expressed in Y59C animals. This suggests a model for the muscle-specific effects: if muscle cell biology is more sensitive to expression of genes embedded in LADs than other tissues, they might be more sensitive to gain-of-function mutants like Y59C. It remains to be seen if these genes are actually retained at the nuclear periphery and if this is the cause of their poor expression.

This worm model for EDMD has raised many interesting questions that will be addressed in future work. Why is the localization and expression of facultative heterochromatin altered in muscle, but not in gut? Is the localization and expression of muscle-specific genes altered in EDMD patients? Finally, how does the phenotype of the Y59C EDMD mutation relate to the phenotypes of other laminopathies, some of which are recessive or have very different phenotypes [7]?

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Stem Cells: Keeping BMP Signaling Local

In stem cell niches, the spatial extent of growth factor signaling needs to be tightly controlled. A new study on the *Drosophila* testicular germline stem cell niche has revealed that BMP signaling is locally activated through linkage to adherens junctions.

Xing Ma and Ting Xie*

Stem cells are almost always associated with so-called niches that regulate stem cell maintenance. Niche-produced short-range signals maintain stem cell self-renewal by directly repressing differentiation, allowing stem cell progeny staying outside the niche to differentiate in an orderly, stepwise manner. In the *Drosophila melanogaster* ovaries and testes, Dpp/BMP, which acts as a long-range morphogen in both wing imaginal discs and the embryo [1], functions as a short-range niche signal to maintain self-renewal of germline stem cells (GSCs) by repressing differentiation-promoting genes such as *bam* [2]. Such short-range BMP signaling maintains a balance between GSC self-renewal and differentiation. Studies on the *Drosophila* ovarian GSC niche have revealed that BMP production and diffusion in the niche cells are tightly controlled in order for BMP to be restricted within the niche [3–8], as BMP expression from outside the GSC niche would otherwise interfere with the normal differentiation of GSC progeny. In addition, BMP signaling in differentiated GSC daughter cells is effectively eliminated by downregulation of BMP signal transducers through differentiation factors [9,10]. These mechanisms restricting BMP signaling to GSCs are likely to also function in the testicular GSC niche. Such short-range effects of niche signals are likely to be a general theme of stem cell control, as stem cells in mammalian tissues must also maintain a steady pool and yet continuously generate the needed differentiated cells. However, precisely how signaling activity is restricted locally is not clear. For instance, in the mammalian hematopoietic system, extracellular matrix, adhesion molecules, secreted signaling molecules and receptors have been proposed to form a synapse-like structure for mediating localized communication at the hematopoietic stem cell–niche interface and achieving stem cell quiescence [11]. Now, a new study by Michel *et al.* [12] has potentially revealed a similar mechanism for restricting BMP